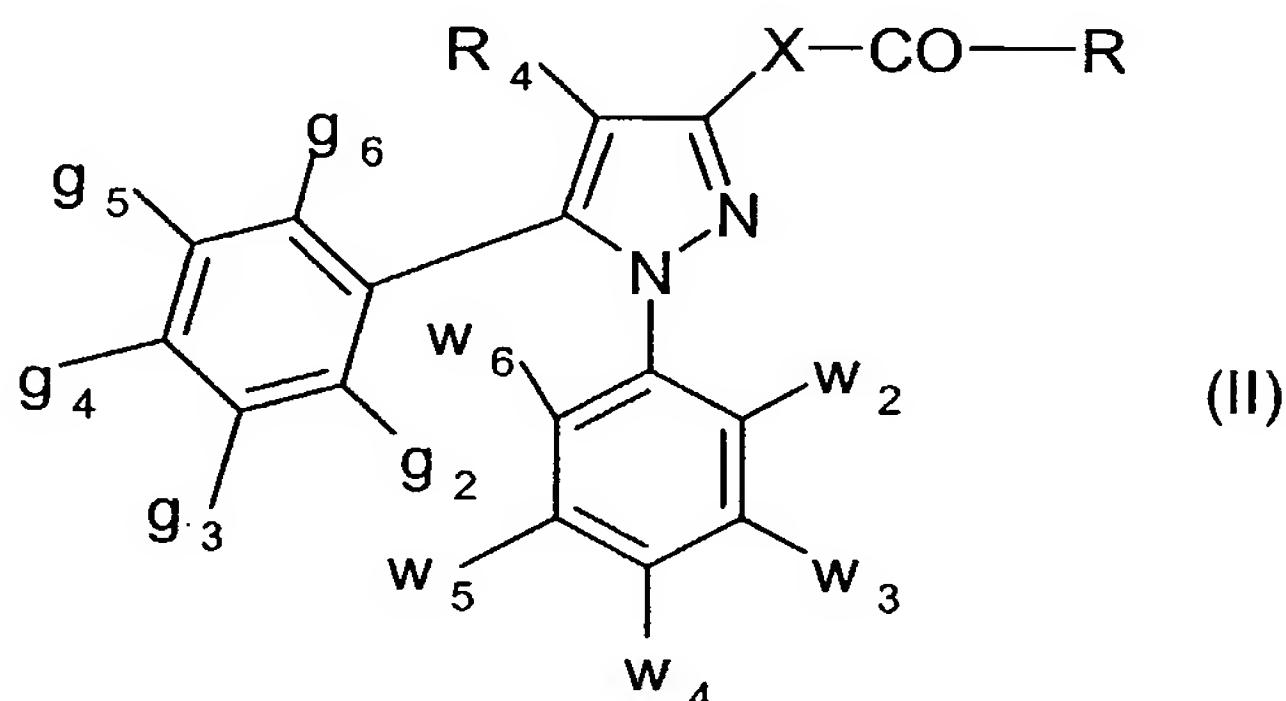


**CLAIMS**

1. Use of an antagonist of the CB1 receptor in the manufacture of a composition for the treatment of hepatic diseases.  
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2. Use according to claim 1 wherein the antagonist of the CB1 receptor is a specific antagonist of the CB1 receptor.
3. Use according to claims 1 or 2 wherein the hepatic disease results in hepatic fibrosis.  
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4. Use according to claims 1 to 3 wherein the hepatic disease is alcoholic liver cirrhosis.
5. Use according to claims 1 to 3 wherein the hepatic disease is chronic viral hepatitis.
- 15 6. Use according to claims 1 to 3 wherein the hepatic disease is non-alcoholic steatohepatitis.
7. Use according to claims 1 to 3 wherein the hepatic disease is primary liver cancer.
- 20 8. Use according to claims 1 to 7 wherein the antagonist is a compound of the formula II or one of its pharmaceutically acceptable salt, in which  $g_2$ ,  $g_3$ ,  $g_4$ ,  $g_5$  and  $g_6$  and  $w_2$ ,  $w_3$ ,  $w_4$ ,  $w_5$  and  $w_6$  are identical or different and are independently hydrogen, a chlorine or bromine atom, a (C<sub>1</sub>-C<sub>3</sub>) alkyl, a (C<sub>1</sub>-C<sub>3</sub>) alkoxy, a trifluoromethyl or a nitro group and  $g_4$  is optionally a phenyl group; R<sub>4</sub> is hydrogen or a (C<sub>1</sub>-C<sub>3</sub>) alkyl; X is either a direct bond or a group -(CH<sub>2</sub>)<sub>x</sub>-N(R<sub>3</sub>)-, in which R<sub>3</sub> is hydrogen or a (C<sub>1</sub>-C<sub>3</sub>) alkyl and x is zero or one; R is: a group -NR<sub>1</sub>R<sub>2</sub> in which R<sub>1</sub> and R<sub>2</sub> are independently a (C<sub>1</sub>-C<sub>6</sub>)-alkyl; an non-aromatic (C<sub>3</sub>-C<sub>15</sub>) carbocyclic radical which is optionally substituted, said substituent(s) being other than a substituted carbonyl; an amino (C<sub>1</sub>-C<sub>4</sub>) alkyl group in which the amino is optionally disubstituted by a (C<sub>1</sub>-C<sub>3</sub>) alkyl; a cycloalkyl (C<sub>1</sub>-C<sub>3</sub>) alkyl in which the cycloalkyl is C<sub>3</sub>-C<sub>12</sub>; a phenyl which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a (C<sub>1</sub>-C<sub>5</sub>) alkyl or by a (C<sub>1</sub>-C<sub>5</sub>) alkoxy; a phenyl (C<sub>1</sub>-C<sub>3</sub>) alkyl; a diphenyl (C<sub>1</sub>-C<sub>3</sub>) alkyl; a naphthyl; an anthracenyl; a saturated 5- to 8-membered heterocyclic radical which is unsubstituted or substituted by a (C<sub>1</sub>-C<sub>3</sub>) alkyl, by a hydroxyl or by a benzyl; a 1-adamantylmethyl; an aromatic heterocycle which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a (C<sub>1</sub>-C<sub>5</sub>) alkyl or by a (C<sub>1</sub>-C<sub>5</sub>) alkoxy; a (C<sub>1</sub>-C<sub>3</sub>) alkyl which is substituted by an aromatic heterocycle which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a (C<sub>1</sub>-C<sub>5</sub>) alkyl or by a (C<sub>1</sub>-C<sub>5</sub>) alkoxy; or else R<sub>1</sub> is hydrogen and R<sub>2</sub> is as  
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defined above; or else R<sub>1</sub> and R<sub>2</sub> form a saturated 5- to 8-membered heterocyclic radical with the nitrogen atom to which they are bonded, said heterocyclic radical being other than morpholine when w<sub>2</sub>, w<sub>3</sub>, w<sub>4</sub>, w<sub>5</sub>, w<sub>6</sub>, g<sub>2</sub>, g<sub>3</sub>, g<sub>4</sub>, g<sub>5</sub> and g<sub>6</sub> are all hydrogen; a group R<sub>2</sub> as defined above when X is -(CH<sub>2</sub>)<sub>x</sub> N(R<sub>3</sub>)-; a group R<sub>5</sub> when X is a direct bond, R<sub>5</sub> being a (C<sub>1</sub>-C<sub>3</sub>) alkyl; a (C<sub>3</sub>-C<sub>12</sub>) cycloalkyl which is unsubstituted or substituted by a (C<sub>1</sub>-C<sub>5</sub>) alkyl; a phenyl (C<sub>1</sub>-C<sub>3</sub>) alkyl which is unsubstituted or substituted by a halogen or by a (C<sub>1</sub>-C<sub>5</sub>) alkyl; a cycloalkyl (C<sub>1</sub>-C<sub>3</sub>) alkyl in which the cycloalkyl is C<sub>3</sub>-C<sub>12</sub> and is unsubstituted or substituted by a (C<sub>1</sub>-C<sub>5</sub>) alkyl; or a 2-norbornylmethyl.



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9. Use according to claims 1 to 7 wherein the antagonist is N-piperidono-3-pyrazolecarboxamide or one of its pharmaceutically acceptable salt.

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10. Use according to claims 1 to 7 wherein the antagonist is N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide or one of its pharmaceutically acceptable salt.

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11. Use according to claims 1 to 7 wherein the antagonist is N-piperidino-5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methylpyrazole-3- carboxamide or one of its pharmaceutically acceptable salt.

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12. Use according to any of the preceding claims wherein the CB1 receptor is selected from the group consisting of:

a) a protein having an amino acid sequence comprising SEQ ID NO:1 or a portion of SEQ ID NO:1, having the biological function of a G protein-coupled cellular receptor, capable of binding THC and transducing a cellular signal;

b) a protein having an amino acid sequence comprising SEQ ID NO:2 or a portion of SEQ ID NO:2, having the biological function of a G protein-coupled cellular receptor, capable of binding THC and transducing a cellular signal;

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- c) an allele of the protein having the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2, having the biological function of a G protein-coupled cellular receptor, capable of binding THC and transducing a cellular signal;
- 5 d) a protein having the amino acid sequence of SEQ ID NO:1 with a Phenylalanine to Leucine substitution at position 200; and/or an Isoleucine to Valine substitution at position 216; and/or a Valine to Alanine substitution at position 246;
- 10 e) a protein having the amino acid sequence of SEQ ID NO:2 with a Phenylalanine to Leucine substitution at position 139; and/or an Isoleucine to Valine substitution at position 155; and/or a Valine to Alanine substitution at position 185; and
- 15 f) a protein comprising the amino acid sequences of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 and SEQ ID NO:9 or amino acid sequences 80 % homologous to these, said protein having the biological function of a G protein-coupled cellular receptor, capable of binding THC and transducing a cellular signal.

13. Use according to claims 1 to 11 wherein the CB1 receptor is a protein having a homology at the amino acid level with SEQ ID NO:1 of at least 45%, having the biological function of a G protein-coupled cellular receptor, capable of binding THC and transducing a cellular signal.

20 14. Use according to the preceding claim wherein the homology is at least 60%, preferably 70 %, more preferably 80 %, even more preferably 90 % and more preferably 95 %.

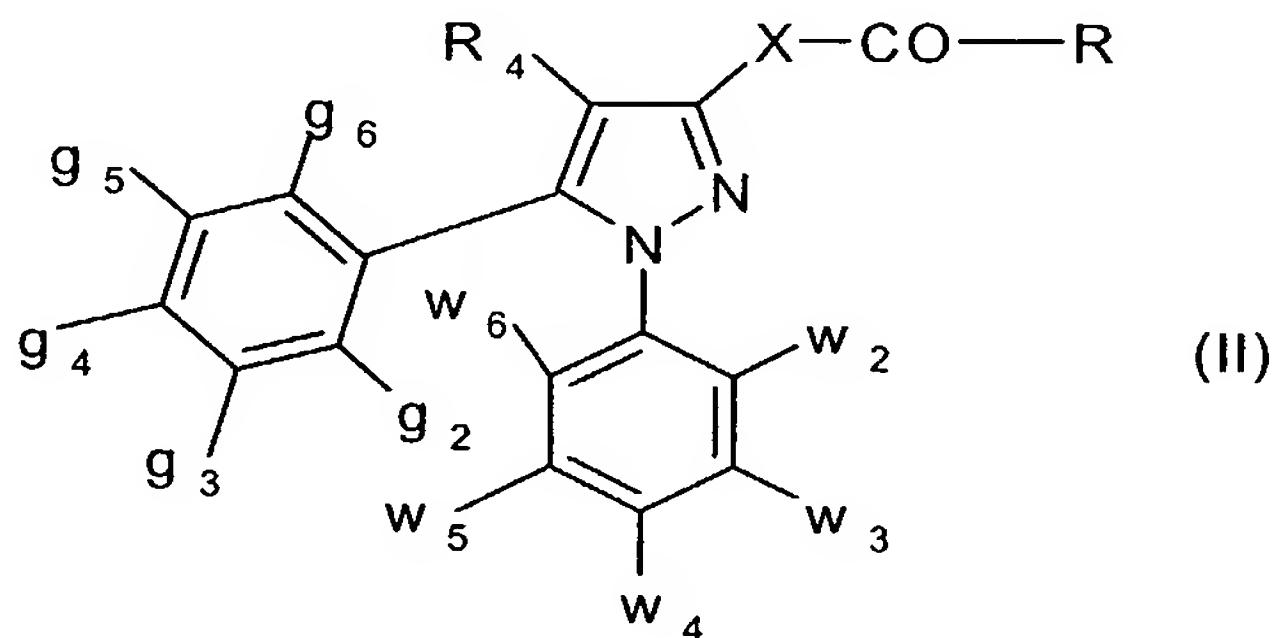
25 15. Use according to any of the preceding claims wherein the daily dosage of CB1 receptor antagonist is from 0.01mg to 500mg, preferably from 1 mg to 100 mg.

30 16. Use of a nucleic acid sequence coding for a protein comprising SEQ ID NO:1 or SEQ ID NO:2 or a portion of SEQ ID NO:1 or a portion of SEQ ID NO:2, for the preparation of a composition for the treatment of hepatic diseases by the downregulation or suppression of the CB1 receptor.

35 17. A method of treatment of hepatic diseases in a mammal comprising the administration of a therapeutically effective amount of at least one CB1 receptor antagonist to a mammal in need thereof.

40 18. A method of treatment of hepatic diseases according to claim 17 wherein the CB1 receptor antagonist is a compound of the formula II or one of its pharmaceutically

acceptable salt, in which  $g_2$ ,  $g_3$ ,  $g_4$ ,  $g_5$  and  $g_6$  and  $w_2$ ,  $w_3$ ,  $w_4$ ,  $w_5$  and  $w_6$  are identical or different and are independently hydrogen, a chlorine or bromine atom, a ( $C_1$ - $C_3$ ) alkyl, a ( $C_1$ - $C_3$ ) alkoxy, a trifluoromethyl or a nitro group and  $g_4$  is optionally a phenyl group;  $R_4$  is hydrogen or a ( $C_1$ - $C_3$ ) alkyl;  $X$  is either a direct bond or a group  $-(CH_2)_x-N(R_3)-$ , in which  $R_3$  is hydrogen or a ( $C_1$ - $C_3$ ) alkyl and  $x$  is zero or one;  $R$  is: a group  $-NR_1R_2$  in which  $R_1$  and  $R_2$  are independently a ( $C_1$ - $C_6$ )-alkyl; an non-aromatic ( $C_3$ - $C_{15}$ ) carbocyclic radical which is optionally substituted, said substituent(s) being other than a substituted carbonyl; an amino ( $C_1$ - $C_4$ ) alkyl group in which the amino is optionally disubstituted by a ( $C_1$ - $C_3$ ) alkyl; a cycloalkyl ( $C_1$ - $C_3$ ) alkyl in which the cycloalkyl is  $C_3$ - $C_{12}$ ; a phenyl which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a ( $C_1$ - $C_5$ ) alkyl or by a ( $C_1$ - $C_5$ ) alkoxy; a phenyl ( $C_1$ - $C_3$ ) alkyl; a diphenyl ( $C_1$ - $C_3$ ) alkyl; a naphthyl; an anthracenyl; a saturated 5- to 8-membered heterocyclic radical which is unsubstituted or substituted by a ( $C_1$ - $C_3$ ) alkyl, by a hydroxyl or by a benzyl; a 1-adamantylmethyl; an aromatic heterocycle which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a ( $C_1$ - $C_5$ ) alkyl or by a ( $C_1$ - $C_5$ ) alkoxy; a ( $C_1$ - $C_3$ ) alkyl which is substituted by an aromatic heterocycle which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a ( $C_1$ - $C_5$ ) alkyl or by a ( $C_1$ - $C_5$ ) alkoxy; or else  $R_1$  is hydrogen and  $R_2$  is as defined above; or else  $R_1$  and  $R_2$  form a saturated 5- to 8-membered heterocyclic radical with the nitrogen atom to which they are bonded, said heterocyclic radical being other than morpholine when  $w_2$ ,  $w_3$ ,  $w_4$ ,  $w_5$ ,  $w_6$ ,  $g_2$ ,  $g_3$ ,  $g_4$ ,  $g_5$  and  $g_6$  are all hydrogen; a group  $R_2$  as defined above when  $X$  is  $-(CH_2)_x-N(R_3)-$ ; a group  $R_5$  when  $X$  is a direct bond,  $R_5$  being a ( $C_1$ - $C_3$ ) alkyl; a ( $C_3$ - $C_{12}$ ) cycloalkyl which is unsubstituted or substituted by a ( $C_1$ - $C_5$ ) alkyl; a phenyl ( $C_1$ - $C_3$ ) alkyl which is unsubstituted or substituted by a halogen or by a ( $C_1$ - $C_5$ ) alkyl; a cycloalkyl ( $C_1$ - $C_3$ ) alkyl in which the cycloalkyl is  $C_3$ - $C_{12}$  and is unsubstituted or substituted by a ( $C_1$ - $C_5$ ) alkyl; or a 2-norbornylmethyl.



19. A method of treatment of hepatic diseases according to claim 17 wherein the CB1 receptor antagonist is N-piperidono-3-pyrazolecarboxamide or one of its pharmaceutically acceptable salt.

20. A method of treatment of hepatic diseases according to claim 17 wherein the CB1 receptor antagonist is N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide or one of its pharmaceutically acceptable salt.

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21. A method of treatment of hepatic diseases according to claim 17 wherein the CB1 receptor antagonist is N-piperidino-5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methylpyrazole-3- carboxamide or one of its pharmaceutically acceptable salt.

10 22. A method of treatment of hepatic diseases according to claims 17 to 21 wherein the hepatic disease is liver fibrosis.

23. A method of treatment of hepatic diseases according to claims 17 to 21 wherein the hepatic disease is alcoholic liver cirrhosis.

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24. A method of treatment of hepatic diseases according to claims 17 to 21 wherein the hepatic disease is chronic viral hepatitis.

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25. A method of treatment of hepatic diseases according to claims 17 to 21 wherein the hepatic disease is non-alcoholic steatohepatitis.

26. A method of treatment of hepatic diseases according to claims 17 to 21 wherein the hepatic disease is primary liver cancer.

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27. A method of treatment of hepatic diseases according to claims 17 to 26 wherein the daily dosage of CB1 receptor antagonist is from 0.01mg to 500mg, preferably from 1 mg to 100 mg.

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